REMARKS/ARGUMENTS

I. Status of the Claims

Claims 9-50 are pending. Claims 1-8 have been canceled. Claims 19-24 and 40 have been withdrawn from examination as drawn to non-elected inventions. Claims 41-50 are added herein.

II. The Present Amendments

No new matter has been added by the present amendments.

New claims 41-50 track current claims 9-17, but recite methods for reducing the infiltration of neutrophils into the lung of a patient suffering from designated conditions. That infiltration of neutrophils into the lungs is reduced by administration of inhibitors of sEH is supported throughout the specification, including page 7, paragraph 0026.

III. The Office Action

The Office Action dated May 18, 2006 (the "Action") rejects the pending claims on several grounds. Applicants traverse the rejections. For the Examiner's convenience, the rejections are discussed below in the order in which they are presented in the Action.

A. Rejection of the claims as allegedly not enabled

The Action rejects claims 9, 10, 14-18, 25, 26, and 30-34 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. Applicants traverse the rejection. The Action's contentions, and Applicants' responses, are set forth below.

1. The Action fails to consider all of the *Wands* Factors

The Action correctly sets forth the eight factors articulated by the Federal Circuit in *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as those that should be considered in determining whether an invention is enabled. Unfortunately, several of the factors are not addressed. There is no evidence on the face of the Action that the rejection has considered at all two of the factors: factor 7, the state of the prior art, and factor 8, the relative skill of those in the art. (The "level of skill in the art" is mentioned once, in the sentence bridging pages 5-6, but as something already considered, without any actual analysis or discussion.) The failure to consider all eight of the factors evidences that the Action has failed to present a *prima facie* case of lack of enablement. As MPEP §2164.01(a) instructs the Examining Corps:

> "It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the [*Wands*] factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole."

Since the Action considers only some of the factors, but ignores others, it fails to meet the requirement of §2164.01(a). For this reason alone, the rejection must be reconsidered.

The failure to consider all of the *Wands* factors is particularly important in the present case, since the Action alleges that there is insufficient guidance to practice the invention as claimed. As the Examiner is aware, the amount of guidance required is inversely related to the degree of skill of those in the art. The persons of skill in the art of treating chronic obstructive pulmonary disease ("COPD") are typically internists or pulmonologists (internists with a subspecialty in lung diseases). Thus, the persons of skill in this art are medical doctors with post-graduate training in the treatment of lung diseases. These highly skilled medical practitioners need relatively little guidance to be able to administer drugs to persons with COPD or how to determine whether to continue treatment with a given therapeutic agent. Accordingly, while the failure to consider all the *Wands* factors would itself be an error requiring withdrawal and reconsideration of the rejection, the failure to consider this factor in this case mandates withdrawal and reconsideration of the rejection.

2. The Analysis of the *Wands* factors

As noted, the Action fails to consider all the *Wands* factors, as required. But, as shown below, the Action also incorrectly analyzes the *Wands* factors it does consider.

(a) The nature of the invention

The Action states that, under the nature of the invention, that the invention "is directed to inhibiting progression in a patient of a respiratory disease[] but has not recited the step(s) that (a) result in inhibiting nor (b) have a specified end result of the treatment." Action, at page 4, item "1".

Contrary to the Action's statement, the claims do recite the step that results in inhibiting progression of the disease: it is the step of administering to the patient an effective amount of an inhibitor of the enzyme soluble epoxide hydrolase ("sEH"). This is the standard method of claiming treatment of disease by administering a composition to a person with the condition. For example, a search of the USPTO patent database simply using the terms "treating" and "disease" resulted in scores of recent patents with claim to treating diseases with phrasing virtually identical to that of the claims under examination, all issued by different examiners examining different disclosures. Claim 1 of U.S. Patent No. 7,105,183, issued September 12, 2006, is illustrative. It reads:

> A method of treating amyotrophic lateral sclerosis (ALS) in a subject, comprising: administering chlorite to a subject having ALS, wherein the chlorite is administered in an amount effective to treat ALS in the subject.

As seen on the face of the claim, the step of the method is administering chlorite, which the patent presumably teaches is useful in treating ALS. Similarly, claim 1 of U.S. Patent No. 7,125,902, issued October 24, 2006, reads:

> A method for the treatment of colon cancer, lung cancer, leukemia, Kaposi's sarcoma, ovarian cancer, sarcoma, meningioma, intestinal cancer, cancer of the lymph nodes, brain tumors, breast cancer, stomach cancer, cancer of the pancreas, cancer of the prostate, and skin cancer comprising administering to a patient or an

animal in need thereof a therapeutically effective amount of a compound having a formula (I): [chemical formula and substituents omitted] or a physiologically tolerable salt thereof.

Once again, the step of the method is the administration of the compound. Nor is the language of these two patents unique or particular to the teachings of the individual specifications. Similar method language is used in, e.g., U.S. Patent No. 7,101,859 (issued September 5, 2006), U.S. Patent No. 7,101,547 (also issued September 5, 2006), U.S. Patent No. 7,112,578 (issued September 26, 2006), and U.S. Patent No. 7,119,085 (issued October 10, 2006). (For the Examiner's convenience, copies of the face page and relevant pages of the claims of each of these patents are enclosed.) The Action sets forth no reason why this language for claiming methods of treatment of disease, repeatedly accepted by the Office, is suddenly not acceptable with respect to the claims under examination.

An examination of the two claims quoted above, as well of the claims of the '859, '547, '578, and '085 patents, also shows that the claims do not recite an endpoint. Presumably, this is because the decision of when to terminate treatment is normally made by the medical doctor treating the patient. As evidenced by the six patents recently issued by the Office and cited above, there is no requirement for an endpoint to be stated in a claim for a method of treatment, and the absence of such a recitation does not affect the ability of the practitioner to make and use the invention.

b. The predictability of the art

The Action makes a series of statements under the general heading of the predictability of the art, for the proposition that the invention is not enabled. As shown below, the statements fail, individually or collectively, to carry the Examiner's burden to set forth a *prima facie* case that the invention is not enabled as claimed.

- First, the Action cites a reference by Bedi, Indian J Chest Allied Sci 47:243-24 (2005) ("Bedi") as assertedly showing that, "even post filing of the current Application, [] there is no silver bullet for COPD and no drug that can prevent same."

The *Wands* factor of predictability in the art is explained by the MPEP, at §2164.03, as follows:

> "The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to the claimed invention pertains, then there is predictability in the art."

Thus, the question of predictability in the art goes to extrapolating from the disclosed results to the invention as claimed. The present specification shows the results of studies in which animals were exposed to tobacco smoke with or without also being administered an exemplar inhibitor of sEH. See, specification, at pages 28-37. Bedi's statement that there is not yet a silver bullet has no obvious relevance to the analysis of whether the results of these studies can be extrapolated to the invention as claimed, as would be relevant to a consideration of predictability under the *Wands* factor. For example, Bedi's statement does not show that there is any variation known in the art in the effect of different inhibitors of sEH in affecting neutrophil infiltration of the lungs, and therefore cannot show that there is any reason why persons of skill would not be able to extrapolate from the results shown in the specification to the invention as claimed. Applicants therefore respectfully maintain that Bedi is irrelevant to the proper analysis of the invention for determining whether the results reported for the invention have predictability for purposes of §112, first paragraph.

- Second, the Action states that "the specification does not provide guidance as to how one skilled in the art would accomplish the objective of inhibition of progression of obstructive pulmonary disease comprising any inhibitor of sEH." Action, at page 4. It is unclear whether the statement is intended to convey that the specification lacks guidance in inhibiting obstructive pulmonary disease, or whether its concern goes to the number of inhibitors of sEH that could be used for inhibiting it under the claims. In either case, the rejection fails to set forth a *prima facie* case of lack of enablement.

As set forth in the MPEP, at §2164.04, the initial burden is on the Examiner to establish a *prima facie* case of lack of enablement:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure).

The present specification presents the results of studies in which animals were exposed to tobacco smoke with or without also being administered an exemplar inhibitor of sEH See, specification, at pages 28-37. When a specification contains *in vivo* animal model assays, those assays constitute "a 'working example' if that example 'correlates' with a disclosed or claimed method invention." MPEP, §2164.02. The Action provides no reason why the animal model assays reported in the specification are not correlated with inhibition of COPD in humans and provides no reason why the results observed in those animal models would differ if other inhibitors of sEH were substituted for the exemplar inhibitor of sEH used in the studies reported in the specification. Accordingly, Applicants respectfully maintain that the Action fails to set forth any cognizable reason why the examples set forth in the application do not enable the invention as claimed.

It is respectfully noted that a simple, unsupported assertion is not sufficient to carry the Examiner's burden. In this regard, MPEP §2164.04 cites *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971):

> As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370.

In the instant case, the Action fails to set forth any reason why there is any unpredictability in the invention as claimed or why the examples set forth in the specification are not sufficient to correlate to the invention as claimed.

- Third, the Action states that there is "no guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for doing same." Action, at page 4. As an initial matter, Applicants note this more properly goes to factor 4, the amount of guidance presented, rather than factor 3, predictability. But, in any event, the analysis is the same. Protocols "to show the efficacy" of a method of treatment are inherently clinical trials. The Examiner is respectfully reminded that proof of the safety and efficacy of therapeutic agent is the province of the Food and Drug Administration, not the Patent and Trademark Office. Just as safety and efficacy are not grounds for Examiners to deny therapeutic utility to an invention under §101 (see, MPEP §2107.01 III. at page 2100-35, right column), they are not themselves a basis for finding that practice of an invention would require undue experimentation. See, MPEP §2107.01 IV. The design and conduct of clinical trials are in any event both well known in the art and irrelevant to the question of enablement since the practitioner following the teachings of the specification can practice the invention.

- Fourth, the Action states that no experimental evidence supporting the contention that the sEH inhibitors would treat COPD by simply administering the compounds. Action, at pages 4-5, bridging paragraph. Applicants respectfully observe that the Action fails to observe that the specification sets forth detailed animal studies in which animals exposed to tobacco smoke were administered an exemplar inhibitor of sEH, and that the animals to which the inhibitor of sEH was administered had lower levels of neutrophils in their lungs than did like animals that were not treated with the sEH inhibitor. See, e.g., specification, at page 37, Table 2 and Figure 4. The specification reports results for studies involving the effect of sEH inhibitors in an animal model of COPD (see, specification, at page 7, paragraph 0026, lines 6-8 of the paragraph). Persons of skill would appreciate, for example, that infiltration of leukocytes into the lungs in response to tobacco smoke is part of the pathology of COPD (see, specification at page 34, paragraph 135), that reducing the number of neutrophils infiltrating into the lungs in response to tobacco smoke therefore reduces the tissue damage to the lungs otherwise expected to occur, and that the results shown in the specification at page 37, Table 2 therefore indicate that there would be reduced damage to the lungs from infiltrating leukocytes. Thus, the data

presented in the specification in fact provide experimental support for the contention that one can treat COPD by administering inhibitors of sEH.

-- Fifth, the Action again states that the claims are not enabled without a specified endpoint. As noted in the section above on the nature of the invention, however, it is routine for method of treatment claims routinely not to state an endpoint, since the decision when to discontinue treatment is in the discretion of the medical practitioner.

Accordingly, taken individually or together, the Action's analysis fails to show that the invention would be unpredictable, and therefore fails to present a proper *prima facie* of lack of enablement.

c. The amount of guidance in the specification

The Action makes the assertion that "the specification does not provide any guidance in terms of inhibition of progressive of obstructive pulmonary diseases comprising any inhibitor of sEH." Action, at page 5.

With respect, the Action's analysis of this *Wands* factor ignores both the examples and the text of the specification. First, as stated above, the specification sets forth detailed animal studies in which animals exposed to tobacco smoke were administered an exemplar inhibitor of sEH. The specification further shows that animals to which the inhibitor of sEH was administered had lower levels of neutrophils in their lungs than did like animals that were not treated with the sEH inhibitor. See, e.g., specification, at page 37, Table 2. Further, the specification sets forth guidance on administering inhibitors of sEH at pages 25-28. Applicants respectfully maintain that, armed with these teachings, the highly skilled practitioners in this art have all the guidance they need to inhibit the progression of COPD using inhibitors of sEH.

d. The presence or absence of working examples

--First, the Action makes the assertion that the specification provides "no working examples" "for inhibition of progression of obstructive pulmonary diseases comprising any inhibitor of sEH for example in a patient." Action, at page 5. The analysis of this *Wands* factor therefore appears to require that a human trial be conducted to show efficacy.

As noted above, the present specification presents the results of studies in which animals were exposed to tobacco smoke with or without also being administered an exemplar inhibitor of sEH. See, specification, at pages 28-37. According to the MPEP, when a specification contains *in vivo* animal model assays, those assays constitute "a 'working example' if that example 'correlates' with a disclosed or claimed method invention." MPEP, §2164.02. The Action provides no reason why the animal model assays reported in the specification are not correlated with inhibition of COPD in humans, and provides no reason why the results observed in those animal models would differ if other inhibitors of sEH were substituted for the exemplar inhibitor of sEH used in the studies reported in the specification. Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. Further, a rigorous or an invariable exact correlation is not required. See, MPEP §2164.02; *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). Accordingly, the Action's assertion that the specification provides no working examples demonstrates that the rejection is based on a misunderstanding of what constitutes a working example for purposes of a *Wands* analysis, and a correspondingly incorrect analysis of this *Wands* factor.

-- Second, the Action states that Applicants have not "disclosed any tests that are highly predictive for the inhibitory effects of the instant compositions. Note that in cases involving physiological activity such as the instant case, 'the scope of enablement obviously varies inversely with the degree of the factors involved.'" Action, at page 5.

Applicants respectfully note that scores of inhibitors of sEH are known in the art, as discussed in the specification at page 13, paragraph 52, to page 16, paragraph 64. There is therefore no unpredictability in the art as to whether there are other compounds that inhibit sEH It is the Applicants' contention that the results shown in the specification in the *in vivo* animal assays with respect to an exemplar sEH inhibitor are due to the activity of the inhibitor on sEH, and that the other known inhibitors of sEH would likewise have the same effect. The Action presents no evidence or reasoning to indicate that there would be any variability if other inhibitors were used, and thus that there is any unpredictability in the effect of sEH inhibitors in inhibiting the progression of COPD.

It is respectfully noted that a simple, unsupported assertion is not sufficient to carry the Examiner's burden to establish there is unpredictability. As already noted above, MPEP §2164.04, quotes *In re Marzocchi* as stating that is necessary for the Examiner to set forth "acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." In the instant case, the Action fails to set forth any evidence or reasoning that shows that persons of skill would expect any different result if a different inhibitor of sEH were used.

e. The quantity of experimentation necessary

The Action conclusorily states that the quantity of experimentation would be undue. Action, at page 5. But, the determination of whether or not the amount of experimentation is or is not undue is a conclusion to be reached after proper consideration of the *Wands* factors. As shown above, the analysis in this Action is flawed on its face, given the failure to consider some of the *Wands* factors and the failure to appreciate the extent of the guidance given in the specification.

The Action further states that to "support a claim to inhibition or the like, Applicant[s] would need to provide confirmative in vivo data supporting the inhibition of progression of the diseases as well as a method and dosage regime resulting in the prevention of same." Action, at page 6. This statement again either ignores the presence of animal assays in the specification, or would require the conduct of a clinical trial. As noted above, the present specification contains *in vivo* animal model assays. The Action provides no reason why the animal model assays reported in the specification are not correlated with inhibition of COPD in humans, and provides no reason why the results observed in those animal models would differ if other inhibitors of sEH were substituted for the exemplar inhibitor of sEH used in the studies reported in the specification. Therefore, the Action's analysis is inconsistent with the requirements of MPEP §2164.02 and must be reconsidered on this basis alone.

3. Conclusion

In sum, the enablement rejection set forth in the Action fails to consider all of the *Wands* factors, fails to note the guidance in the specification, fails to note the in vivo animal assays which persons of skill would understand as predictive of success in inhibiting progression of COPD in humans, fails to set forth reasoning or evidence that there is unpredictability in the art, and improperly would require clinical testing in humans without a showing that the animal assays reported in the specification are not correlated with success in using the inhibitors in humans. For all these reasons, the rejection should be reconsidered and, Applicants maintain, withdrawn.

B. Rejection of the claims as allegedly anticipated

Claims 9, 10, and 14 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Morisseau et al., Proc Natl Acad Sci 96:8849-8854 (1996) ("Morisseau"). According to the Action, Morisseau teaches "that treatment with compounds such as DCU . . . reduce the toxicity of leukotoxin in mice and prevent symptoms suggestive of acute respiratory distress syndrome (in current claims 9-10 and 14 . . .). Action, at page 7. Applicants traverse.

As the MPEP states, at §2131, "[a] claim is anticipated on if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §21321, quoting *Verdegaal Bros v. Union Oil Co. of California*, 814 F.2d 628, 631 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Acute respiratory distress syndrome is not the same disease or syndrome as COPD, and the Action does not even allege a connection between the two diseases. The Action thus fails to show that Morisseau contains each and every element of the claims under examination. Accordingly, the Action has failed to present a proper prima facie case of anticipation. The rejection should be reconsidered and, Applicants maintain, upon reconsideration, withdrawn.

C. Rejection of the claims as allegedly obvious

Claims 9, 14-18, 25, 26, and 30-34 are rejected under 35 U.S.C. § 103(a) as allegedly anticipated by Morisseau in view of Fang et al., J Biol Chem 276:14867-74 (2001) ("Fang"). According to the Action, Morisseau teaches "that treatment with compounds such as DCU . . . reduce the toxicity of leukotoxin in mice and prevent symptoms suggestive of acute respiratory distress syndrome (in current claims 9-10 and 14 . . .), while Fang is cited as teaching "that EETs have anti-inflammatory properties (in current claims 25-26 and 30-34 . . .). Action, at pages 8-9. The Action alleges that persons of skill would have been motivated to combine Morisseau with Fang because combining two agents with anti-inflammatory effects is prima facie obvious. Applicants traverse.

The Action fails to set forth a proper prima facie case of obviousness. As noted in the preceding section, acute respiratory distress syndrome is not the same disease or syndrome as COPD, and the Action does not even allege a connection between the two diseases. There is therefore no logical nexus between the teachings of Morisseau and the invention as claimed. The Action wholly fails to explain why the artisan would choose to combine these references to treat a condition that the Action has not even alleged to be related to those discussed in the reference.

Fang does not cure this deficit. Fang is primarily directed to the effects of EETs on endothelial cells in the vasculature. Thus, any motivation to combine Fang's teachings regarding EETs for treating COPD must come from Morisseau. And, as noted, the Action provides no logical nexus between the condition discussed in Morisseau and those that are the subject of the claims under examination.

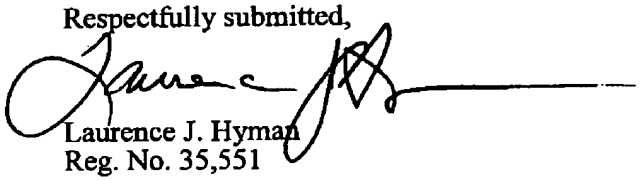
Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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